III. Remarks

A. Amendments to the Claims

Applicants have amended claims 8-9, 13-16 and 20-25 to provide that the suspension is no longer comprised of fluoride calcium salts and that the precipitation reaction is no longer prepared from aqueous solutions of water-soluble fluoride salts. Support for the amendment is provided in the Specification at page 7, line 19, to page 8, line 4.

Applicants have amended claim 9 to further define the particles of the suspension as comprising calcium salts in the form of primary particles and a defined colloid which is adsorbed onto the primary particles. Support for the amendments is provided in the Specification at page 3, line 32, to page 4, line 7.

B. Rejections Under 35 U.S.C. Section 112 — Written Description Requirement

1. Examiner's Reasons for the Rejection

> Claims 8, 9, 13-16 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite the limitation "acidic aqueous solution of water-soluble calcium salts and aqueous solutions of water-soluble phosphate or fluoride salts at increased pH using an aqueous alkali ammonia and in the presence of." The specification does not appear to support solutions of fluoride salts being utilized in this method.

(Examiner's Action, page 2, lines 11-19).

2. Applicants' response to the rejection

As noted above, Applicants have amended pending claims 8–9, 13–16 and 20–25 to provide that the claims no longer refer to solutions of fluoride salts in the general recitation of "aqueous solutions of water-soluble phosphate or fluoride salts." Applicants have also amended the pending claims to remove the reference that the suspension may be of fluoride calcium salts.

In view of these amendments, Applicants believe that the rejection of claims 8, 9, 13–16 and 20–25 under 35 U.S.C. Section 112, first paragraph, has become moot and should be withdrawn.

C. Rejections Under 35 U.S.C. Section 103 — Obviousness

Claims 8, 9, 13–16 and 20–25 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al., in view of United States Patent No. 5,560,932 to Bagchi et al.

1. Examiner's reasons for the rejection

The Examiner's reasons for the rejection are set forth in the Action in the "Examiner's Response to Applicant's Arguments" and in the "Examiner's Response to the Declaration." For convenient reference these responses are reproduced below:

Examiner's Response to Applicant's Arguments

> Although the hydroxyapatite of Rudin are pure hydroxyapatite, the teachings of Bagchi et al. would motivate one of ordinary skill in the art to coat the hydroxyapatite to inhibit aggregation due to inter-particle attractive forces. In regards to the method of making the colloidal system, the instant disclosure teaches several ways to make the colloidal systems of the instant claims. (See page 7 of the instant specification). It appears not all of the methods of making the product of the instant claims required one initial acidic solution in order to make the compositions of the instant claims. Further, the product of the instant claims and the product of the combined reference have the same function as being used in an oral composition and restoring dental enamel. The prior art product appears to differ from the claim product only in the method of obtaining the product. The burden of persuasion is on Applicant to show that the claimed product exhibits

> unexpected properties compared with that of the prior art. See MPEP 2144.04. Although Applicant asserts a material with different properties is yielded from the procedures of the instant claims than what is taught in the combination of references, there appears to be no evidence to support [the contention] that the compositions have different properties provided in the instant disclosure or the filed Declarations. Note that the burden is higher for applicant due to the "peculiar nature" of product by process claims, as discussed therein.

(Examiner's Action, page 3, line 17, to page 4, line 15).

Examiner's Response to the Declaration

> As mentioned above, although the hydroxyapatite of Rudin et al. is pure, the combined teachings of Rudin et al. and Bagchi et al. suggest the compositions of the instant claims. Although the methods of making the compositions vary and Applicant asserts the instant compositions have different properties than the properties disclosed by Bagchi et al., Applicant has provided no objective evidence to support this assertion. It cannot be determined, without a evidence if the products from the different methods yield products with different properties such as the intermolecular cross-linkages between the hydroxyapatite and the coating.

(Examiner's Action, page 5, lines 14–21).

2. Legal standard for determining whether Applicants' claims are obvious under 35 U.S.C. Section 103

The legal interpretation of Section 103 to be applied is set forth in the recent Supreme Court decision of *KSR International Co. v. Teleflex Inc.* (*KSR*), 550 U.S. __, 82 USPQ2d 1385 (2007). *KSR* cites *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 148 USPQ 459 (1966) as setting out an objective analysis for applying Section 103. (82 USPQ2d at 1388). The objective analysis is as follows:

> Under § 103, the scope and content of the prior art are to be determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

(148 USPQ at 467).

Accordingly, the factual inquiries set forth by the Court are as follows:

- [T]he scope and content of the prior art are . . . determined;
- Differences between the prior art and the claims at issue are . . . ascertained;
- The level of ordinary skill in the prior art [is] resolved; and
- Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized. . . .

3. Application of the *Graham v. John Deere Co.*, factual standards

The application of the *Graham v. John Deere Co.* factual standards is being made in conjunction with the Third and Fourth Declarations of Dr. Christian Kropf, one of the inventors of the invention disclosed and claimed in this application.

(The Third Declaration of Dr. Christian Kropf was originally filed on February 4, 2008, with Applicants' Amendment and Response and marked as EXHIBIT B to it. The Fourth Declaration of Dr. Christian Kropf was originally filed on September 30, 2008, with Applicants' Amendment and Response and marked as EXHIBIT B to it.)

For the filing of Applicants' present Amendment and Response, the Third Declaration of Dr. Christian Kropf is marked as EXHIBIT A and the Fourth Declaration of Dr. Christian Kropf is marked as EXHIBIT B.

(a) Determining the scope and content of the prior art

The Rudin et al. patent discloses a composition characterized in that it comprises particles of hydroxyapatite with an average particle size in length (l), width (d), and thickness (h). The values for these dimensions are: (l) from 0.2 μm to 0.01 μm, (d) 0.1 μm to about 0.001 μm and (h) from 0.1 μm to 0.0001 μm (column 2, lines 22-27) (Third Declaration of Christian Kropf, Paragraph 5).

Rudin et al. further discloses that the hydroxyapatite being introduced into the composition possesses osteo-reparative properties and contains preferably about 100% $Ca_{10}(PO_4)_6(OH)_2$ and that the specific surface of hydroxyapatite used in the composite advantageously is 100 to 150 m^2/g (column 2, lines 41-45). This disclosure indicates that the hydroxyapatite disclosed in Rudin et al. is pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraph 6).

Rudin et al. further discloses an oral product that will comprise a liquid phase containing humectants and binding thickeners which act to maintain the particulate solid abrasive and hydroxyapatite crystals in the form of stable suspension in liquid phase (column 3, lines 11-15). On the basis of the disclosure in Rudin et al., the hydroxyapatite crystals in the suspension are pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraphs 6 and 7).

The conclusion that the hydroxyapatite particles disclosed in Rudin et al. are pure is further based on the disclosure at column 2, lines 46-51 of Rudin et al. that U.S. Patent No. 6,254,855 B1 describes a method for producing a suspension of hydroxyapatite as described in the Rudin et al. application. U.S. Patent No. 6,254,855 B1 discloses in EXAMPLE 1 that according to the method described in that patent, a pure stochiometric hydroxylapatite in a suspension form is produced free of admixtures (column 3, lines 43-67) (Third Declaration of Christian Kropf, Paragraph 8).

The Bagchi et al. patent describes the preparation of a nanoparticulate dispersion and the resulting nanoparticles. The process is summarized in the Abstract, the pertinent portion of which is set forth below.

> This invention describes the preparation of nanoparticulate pharmaceutical agent dispersion via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of a suitable surface-modifying, surface-active agent to form a fine particle dispersion of the said pharmaceutical agent.

(Fourth Declaration of Christian Kropf, Paragraph 5).

Bagchi et al. discloses the objective of the invention at column 3, lines 7–16, which is quoted herebelow:

> It would be desirable to provide stable dispersible drug or pharmaceutical agent particles in submicron size range which can be readily prepared which do not appreciably flocculate or agglomerate due to interparticle attraction forces, and do not require the presence of a crosslinked matrix, simultaneously providing enhanced bioavailability of the drug. Furthermore, it would be highly desirable that such formulations do not involve removal of toxic residues such as toxic solvents or heavy metal solubilizates that arise out of attrition of the milling media.

(Fourth Declaration of Christian Kropf, Paragraph 6).

The accomplishment of this objective by the Bagchi et al. invention is referred to in the following description of the advantages of the invention.

> It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention. (Column 3, lines 50-52).
>
> A further advantage of the method is that unlike solvent precipitation, the final product of this invention is free of any trace of trace solvents that may be toxic and must be removed by expensive treatments prior to final product formulation. (Column 4, lines 7-11).

(Fourth Declaration of Christian Kropf, Paragraph 7).

The particles of the invention, the process of making the particles and a preferred utility are disclosed in the paragraph directly under the heading "Description of Preferred Embodiments." That paragraph is set forth below.

> This invention is based partly on the discovery that pharmaceutical agent particles having an extremely small effective average particle size can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier, and that such particles are stable and do not appreciably flocculate or aggregate due to interparticle attractive force and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. (Column 4, lines 40-48).

(Fourth Declaration of Christian Kropf, Paragraph 8).

Bagchi et al. discloses that the particles comprise a pharmaceutical agent substance in a discrete crystalline phase. (Column 4, lines 56-61) (Fourth Declaration of Christian Kropf, Paragraph 9).

Bagchi et al. discloses that the surface modifier adheres to the surface of the particles but is free of intermolecular linkages between the molecules of the modifier, and between the modifier and the particles, due to the lack of chemical bonds between the surface modifier and [drug] particle. This disclosure in Bagchi et al. is set forth at column 5, lines 43–46 and in the passage herebelow:

> The surface modifier is adsorbed on the surface of the pharmaceutical agent in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. (Column 6, lines 20–26).

(Fourth Declaration of Christian Kropf, Paragraph 10).

(b) Ascertaining the differences
between the prior art and the claims at issue

Claim 8 of the application is directed to a suspension. The remaining claims 9, 13–16 and 20–25 are directed to a toothpaste comprising the suspension, or other suspensions within the scope of claim 8. Claim 8 reads as follows:

> Claim 8. A suspension of one or more phosphate calcium salts, or fluorophosphate calcium salts in a liquid medium in which the salts are less than 1 g/l soluble, wherein the calcium salts comprise primary particles having diameters of from 5 to 50 nanometers and lengths of from 10 to 150 nanometers, wherein the calcium salts are formed by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate salts at an increased pH using an aqueous alkali or ammonia and in the presence of a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble polymeric protective colloid selected from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropylguar, resulting in the colloid being adsorbed onto said particles and the particles being stabilized against agglomeration.

A comparison of the suspension claimed in Claim 8 with the suspension disclosed in Rudin et al. reveals that the claimed suspension is distinct from the suspension taught or suggested by Rudin et al. Rudin et al. discloses crystals of pure hydroxyapatite of a defined particle size that are maintained in a suspension. Applicants' claimed suspension is of particles of calcium salts, wherein a defined water-soluble polymeric protective colloid, in particular, gelatin, is adsorbed onto said particles. Accordingly, Rudin et al. does not disclose or suggest Applicants' claimed suspension comprising particles of one or more calcium salts with a colloid (gelatin) adsorbed onto said particles, which is set forth in all of Applicants' pending claims 8–9, 13–16 and 20–25.

Applicants' process of making the particles is different from the process used to make the Bagchi et al. particles. Applicants' process as disclosed in the Specification at page 7, lines 13–19, prepares the claimed suspensions by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate salts in the presence of water-soluble polymeric protective colloids. Applicants' precipitation reactions are carried out at an increased pH using an aqueous alkali or ammonia. The Bagchi et al. process begins with the dissolution of a pharmaceutical agent in an aqueous base and the addition of an aqueous surfactant solution followed by the addition of an acid solution to form a nanoparticulate dispersion. *See* Steps 1–3 on the cover sheet of the Bagchi et al. patent. As noted above in Paragraph 8, the Bagchi et al. particles can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier.

Unlike the Bagchi et al. process in which the particles are formed by homogeneous nucleation, the calcium salt particles of Applicants' claimed suspension are formed from precipitation reactions of acidic aqueous solutions of water-soluble calcium salts and of aqueous solutions of water-soluble phosphate salts. Applicants' precipitation reactions occur under conditions of increasing pH using an aqueous alkali or ammonia in the presence of one or more of Applicants' claimed colloids rather than under conditions of decreasing pH as disclosed in Bagchi et al. Applicants' precipitation reactions of acidic aqueous solutions of water-soluble calcium and phosphate or fluoride salts, in the presence of the colloid, and at an increasing pH, results in particles having a more intense structure in which, in Applicants' claimed particles, the colloid forms

intermolecular crosslinkages. In contrast, in the Bagchi et al. particles, the surface modifiers (*i.e.*, colloid) are essentially free of intermolecular crosslinkages.

Accordingly, the disclosure of Bagchi et al. relied upon by the Examiner, *i.e.*, the absence of intermolecular, *i.e.*, interparticle attractive, forces and chemical bonding between the surface modifiers and the surface modifiers and particles to avoid the aggregation of small particles. The Bagchi et al. disclosure teaches away from Applicants' claimed particles, which are chemically bonded to the colloid and possess intermolecular crosslinkages.

Hence, the Bagchi disclosure has very little relevance to Applicants' claimed suspension.

(c) Resolving level of ordinary skill in pertinent art

The inventors of the present application, one of whom is Dr. Christian Kropf, and the inventors of the Rudin et al. and Bagchi et al. patents, would represent persons of ordinary skill in the art.

(d) Utilizing such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*

Rudin et al. and Bagchi et al. have failed exemplify, disclose or suggest to one of ordinary skill in the art, Applicants' claimed suspension of poorly water-soluble calcium salts in finely divided form, which are stabilized during precipitation. *See* Specification at page 3, lines 25–30.

4. Applicants' claims are patentable over Bagchi et al.

As noted above, Applicants disclose and claim a suspension of particles which are modified and stabilized against coagulation and agglomeration by a water-soluble protective colloid adsorbed onto the particles. Applicants' modified and stabilized particles constitute particles having intermolecular crosslinkages. Bagchi et al. discloses that its particles and surface modifier are essentially free of intermolecular crosslinkages.

Accordingly, one of ordinary skill in the art could not derive Applicants' claimed suspension of particles from Bagchi et al. Therefore, Rudin et al. and Bagchi et al. fail to recognize, let alone exemplify, disclose or even suggest to one of ordinary skill in the art the suspension set forth in all of Applicants' claims 8–9, 13–16 and 20–25.

Accordingly, for the reasons set forth above, the rejection of claims 8–9, 13–16 and 20–25 under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al. in view of United States Patent No. 5,560,932 to Bagchi et al. is untenable and should be withdrawn.

IV. Conclusion

It is believed that the above Amendment and Remarks constitute a complete response under 37 C.F.R. Section 1.111 and that all bases of rejection in the Examiner's Action have been adequately rebutted or overcome. A Notice of Allowance in the next Office Action is, therefore, respectfully requested. The Examiner is requested to telephone the undersigned attorney if any matter that can be expected to be resolved in a telephone interview is believed to impede the allowance of pending claims 8-9, 13-16 and 20-25 of United States Patent Application Serial No. 09/868,379.

Respectfully submitted,

PAUL AND PAUL

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/John S. Child, Jr./
John S. Child, Jr.
Registration No. 28833
2000 Market Street
Suite 2900
Philadelphia, PA 19103-3229
Telephone: (215) 568-4900
Facsimile: (215) 567-5057
Attorneys for Applicants

CORRESPONDENCE ADDRESS
Customer No. 55495
Paul and Paul
2000 Market Street
Suite 2900
Philadelphia, PA 19103-3229
Paul and Paul Order No. 7405